

**UCSD Human Research Protections Program  
New Biomedical Application  
RESEARCH PLAN**

Instructions for completing the Research Plan are available on the [HRPP website](#).  
The headings on this set of instructions correspond to the headings of the Research Plan.  
General Instructions: Enter a response for all topic headings.  
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 6/21/2018

**1. PROJECT TITLE**

**A Randomized, Subject-Masked, Active-Controlled, Parallel-Arm Clinical Trial Comparing Erector Spinae and Paravertebral Nerve Blocks**

**2. PRINCIPAL INVESTIGATOR**

Brian M. Ilfeld, MD, MS

**3. FACILITIES**

UCSD hospitals and the UCSD CTRI

**4. ESTIMATED DURATION OF THE STUDY**

Three years (1 month preparation, 24 months enrollment, 11 months publication prior to closure)

**5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)**

Following painful surgical procedures of the breast, postoperative analgesia is often provided with a paravertebral nerve block (PVB). For intense, but shorter-duration acute pain, a single-injection of local anesthetic is used with a duration of approximately 12 hours. Recently an alternative block has been reported: the erector spinae plane block.<sup>2</sup> The theoretical benefits include ease of administration since it is a plane superficial to the PVB and therefore easier to identify and target with ultrasound (therefore increasing success rate); and an increased safety margin as there are fewer anatomic structures in the immediate area which could be injured with the needle; and, the target plane is much further from the intrathecal/epidural space relative to the PVB, therefore leakage of cerebrospinal fluid or injury to the spinal cord are less likely with the erector spinae compared to the PVB.<sup>3</sup> There are, therefore, multiple theoretical reasons to prefer the erector spinae over the PVB. Unfortunately, it remains unknown if the analgesia provided by this new technique is comparable to that provided with the PVB.<sup>4</sup> We therefore propose to compare these two techniques with a randomized, subject-masked, active-controlled, parallel-arm clinical trial.

**6. SPECIFIC AIMS**

The overall objective of the proposed research is to determine the relative risks and benefits of erector spinae plane versus paravertebral blocks for single-injection local anesthetic administration.

**Hypothesis 1:** Following breast surgery, **analgesia** will be non-inferior in the recovery room with an erector spinae plane block compared with a paravertebral block as measured with the Numeric Rating Scale.

**Hypothesis 2:** For breast surgery, **opioid** consumption will be non-inferior in the operating and recovery rooms with an erector spinae plane block compared with a paravertebral block (primary: cumulative intravenous morphine equivalents).

**Primary end point:** *In order to claim that erector spinae plane blocks are non-inferior to paravertebral blocks, both Hypotheses 1 and 2 must be at least non-inferior.*

**7. BACKGROUND AND SIGNIFICANCE**

Following painful surgical procedures of the breast, postoperative analgesia is often provided with a

paravertebral nerve block (PVB). For intense, but shorter-duration acute pain, a single-injection of local anesthetic is used with a duration of approximately 12 hours. The PVB has several limitations: it can decrease blood pressure, and very rare—but serious—complications have occurred, including neuraxial injection, neuraxial hematoma, and pleural puncture.<sup>1</sup> An alternative block has been described: the erector spinae plane block.<sup>2</sup> The theoretical benefits include ease of administration since it is a plane superficial to the PVB and therefore easier to identify and target with ultrasound (therefore increasing success rate); and an increased safety margin: there are few anatomic structures in the immediate area which could be injured with the needle; and, the target plane is much further from the intrathecal/epidural space relative to the PVB. Lastly, the plane may be easier to catheterize for continuous peripheral nerve blocks relative to the relatively-small volume PVB.<sup>3</sup>

There are therefore multiple *theoretical* reasons to prefer the erector spinae plane block. Unfortunately, it remains unknown if the analgesia provided by this new technique is comparable to that provided with the PVB.<sup>4</sup> We therefore propose to compare these two techniques with a randomized, subject-masked, active-controlled, parallel-arm, human subjects clinical trial.

## 8. PROGRESS REPORT

There are no preliminary or pilot study data.

## 9. RESEARCH DESIGN AND METHODS

This investigation will be a randomized, subject-masked, active-controlled parallel-arm, human subjects clinical trial. Of note, we will be using standard-of-care local anesthetic under an FDA-approved purpose and do not plan to research a possible change of indication or use of these medications as part of this research project. The treatments in both groups are currently used at our institution and there is true clinical equipoise at this time. The only difference in treatment between subjects who enroll versus those not enrolled in this study will be those who enroll will have the decision between which anatomic block location determined randomly, as opposed to the physician simply choosing him/herself.

**Enrollment.** Consenting adults undergoing breast surgery with a planned single-injection regional analgesic will be offered enrollment. Patients undergoing breast surgery with a planned perineural catheter regional analgesic will be excluded. Study inclusion will be proposed to eligible patients prior to surgery. If a patient desires study participation, written, informed consent will be obtained using a current UCSD IRB-approved ICF. Selection for inclusion will not be based on gender, race, or socioeconomic status. The study population of interest includes men and women of all races and socioeconomic status. Inclusion and exclusion criteria are listed in section #9 below.

**Preoperative Procedures.** Following written, informed consent, we will collect baseline anthropomorphic information (e.g., age, sex, height, and weight). All subjects will have a peripheral intravenous (IV) catheter inserted, standard noninvasive monitors applied, supplemental oxygen administered via a nasal cannula or face mask, and placed in the sitting position. Midazolam and fentanyl (IV) will be titrated for patient comfort, while ensuring that patients remain responsive to verbal cues. Both possible block locations will be viewed with ultrasound. If one or both of the locations is unacceptable for block placement in the clinician's opinion, the subject will not be randomized and will not proceed further with the study.

Subjects will then be randomized using a computer-generated list and opaque, sealed envelopes to

one of two treatment groups: (blocks of 4, stratified for unilateral vs. bilateral surgery): (1) erector spinae plane or (2) paravertebral block. All blocks will be placed by a regional anesthesia fellow or resident under the direct supervision and guidance of a regional anesthesia attending (or by the attending him/herself).

The area of needle insertion will be cleaned with chlorhexidine gluconate and isopropyl alcohol. All blocks will be placed using standard UCSD ultrasound-guided techniques as previously described.<sup>4,5</sup>

Ropivacaine 0.5% (with epinephrine 1:200,000-400,000) will be administered via the needle into the target plane. For erector spinae plane blocks, this will be at the T3 level for surgery involving the axilla and the T4 level for surgery not involving the axilla (20 mL of local anesthetic for unilateral surgery; 16 mL of local anesthetic each side for bilateral surgery). For PVBs without axillary work, this will be at the T3 and T5 levels. For PVBs with axillary work, this will be at the T2 and T4 levels. For unilateral PVBs, 10 mL of local anesthetic will be injected per level. For bilateral PVBs, 8 mL of local anesthetic will be injected per level.

Single-injection blocks will be considered successful if, within 30 minutes, the subject experiences decreased sensation to cold temperature with an alcohol pad over the approximate level of the ipsilateral 4th thoracic dermatome. Misplaced blocks will be replaced successfully, or the patient excluded from further study participation. For subjects undergoing bilateral surgical procedures, a block using the same protocol will be administered on the contralateral side.

Intraoperatively, all subjects will receive a general anesthetic using inhaled and intravenous anesthetic and oxygen. Intravenous fentanyl will be administered for cardiovascular responsiveness to noxious stimuli at the discretion of the anesthesia provider.

**Postop:** Subjects will be discharged with a prescription for oxycodone 5 mg tablets for supplementary analgesia and instructed to record the time at which they take their first opioid tablet as well as the time at which they believe the block starts to wear off.

**Outcome measurements (end points).** Pain scores will be recorded using the NRS. Within the recovery room, pain scores, opioid requirements, and antiemetic administration will be recorded by nursing staff masked to treatment group. The morning following surgery, all subjects will be contacted by phone or in person [if hospitalized] to record lowest, average, highest, and current pain scores; sleep disturbances, and nausea using a 0-10 Likert scale (0 = no nausea; 10 = vomiting). For outpatients, opioid requirements will be recorded while inpatients will have opioid requirements extracted from the electronic medical record. In addition, we will extract antiemetic use from the electronic record. We will collect the times at which subjects felt their block resolve and they consumed their first opioid analgesic pills following recovery room discharge.

**Hypothesis 1:** Following breast surgery, **analgesia** will be non-inferior in the recovery room with an erector spinae plane block compared with a paravertebral block as measured with the Numeric Rating Scale.

**Hypothesis 2:** For breast surgery, **opioid** consumption will be non-inferior in the operating and recovery rooms with an erector spinae plane block compared with a paravertebral block (primary: cumulative intravenous morphine equivalents).

**Primary end point:** *In order to claim that erector spinae plane blocks are non-inferior to paravertebral*

*blocks, both Hypotheses 1 and 2 must be at least non-inferior.*

**Statistical methods.** Descriptive statistics will be provided by arm and in aggregate. Baseline characteristics of arms will be compared using the Wilcoxon-Mann-Whitney and Fisher's Exact tests. Key characteristics that are significantly different ( $p < 0.05$ ) will be included as covariates in the analysis models.

**Primary aim.** We will test the noninferiority of the erector spinae nerve block compared to the paravertebral nerve block. The 95% confidence interval (CI) associated with the Wilcoxon-Mann-Whitney test will be derived for the group difference (paravertebral minus erector spinae) in median pain scores within the recovery room. If the lower limit of the 95% CI is greater than -1.25, we will conclude noninferiority. If there are significant differences between the groups in any key characteristics, these characteristics will be included as covariates in a linear model. The same noninferiority margin (-1.25) will be applied to the 95% CI for the covariate adjusted group difference in mean pain derived from the linear model.

The noninferiority of the erector spinae nerve block with regard to total opioid consumption within the operating and recovery rooms will be tested in the same manner as pain, i.e. comparing the limits of a 95% CI associated with the Wilcoxon-Mann-Whitney test to a predefined noninferiority margin (in this case 2 mg). Covariate adjusted linear models will again be applied in the event that key characteristics are significantly different between the groups.

**Sample size justification.** Power for the Wilcoxon-Mann-Whitney derived noninferiority testing is based on 10,000 simulated trials. We simulated pain scores from a discrete distribution with median (interquartile range) 3 (2-5) [Kairaluoma, 2004]. Between the quartiles, the probability of each score was assumed constant. The distribution for each group was assumed to be the same. The sample size of  $n=50$  per group provides 82% power to detect noninferiority in pain with a margin of 1.25. Similarly, opioid consumption was assumed to follow a truncated normal distribution with mean 2.5 mg and standard deviation 2 mg, and minimum value 0 mg. The sample size of  $n = 50$  per group provides at least 95% power to detect noninferiority with margin 2 mg. Therefore, we will enroll 50 subjects for each of two treatments with a total enrollment of 100 subjects. To allow for dropouts, we will request a maximum enrollment of 120 subjects. Noninferiority in pain is tested first, and if significant, noninferiority in opioid consumption is tested. Under this hierarchical testing framework, no adjustment in alpha is necessary to control Type 1 error [Mascha, et al 2012].

## 10. HUMAN SUBJECTS

**Inclusion criteria for the trial will be:** (1) undergoing unilateral or bilateral breast surgery with at least moderate postoperative pain anticipated; (2) analgesic plan includes a single-injection peripheral nerve block(s); and (3) age 18 years or older.

**Exclusion criteria for the trial will be:** (1) morbid obesity as defined by a body mass index  $> 40$  ( $BMI = \text{weight in kg} / [\text{height in meters}]^2$ ); (2) renal insufficiency (preoperative creatinine  $> 1.5$  mg/dL); (3) chronic opioid use (daily use within the 2 weeks prior to surgery and duration of use  $> 4$  weeks); (4) history of opioid abuse; (5) any comorbidity which results in moderate or severe functional

limitation; (6) inability to communicate with the investigators or hospital staff; (7) pregnancy; (8) planned regional analgesic with perineural catheter placement; and (9) incarceration. We will recruit a maximum of 120 subjects. Selection for inclusion will not be based on race or socioeconomic status. The study population of interest includes men and women of all races and socioeconomic status. There will be no participants from vulnerable populations, such as pregnant women, children, or prisoners.

#### **11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH**

Study inclusion will be proposed to eligible patients prior to surgery by the investigators. Since the investigators will be contacting patients as part of their standard preoperative anesthesia consultation, HIPAA regulations will be adhered to. For women of childbearing age with the possibility of pregnancy, a sample of urine is always collected for a pregnancy test prior to surgery—regardless of study participation. Pregnant patients will be excluded from study participation.

#### **12. INFORMED CONSENT**

If a patient desires study participation, written, informed consent will be obtained. An investigator or research assistant/coordinator (including regional anesthesia fellows) specifically trained in both study details and appropriate consenting procedures will attain verbal and written informed subject consent. The method of documenting consent will be using written informed consent form (including a written HIPAA consent form and UCSD Experimental Subjects' Bill of Rights).

#### **13. ALTERNATIVES TO STUDY PARTICIPATION**

If a patient declines enrollment, s/he will receive their perioperative analgesic with the choice of which anatomic location to use (erector spinae plane or paravertebral block) determined by the attending regional anesthesiologist instead of randomly per study protocol.

#### **14. POTENTIAL RISKS**

Patients offered participation in this study are already planning on having a regional analgesic for postoperative analgesia, so the risks of having this type of analgesic modality are not affected by study participation. Currently, it remains unknown whether or not there are relatively higher risks with one anatomic location over the other. There is, however, the risk of loss of confidentiality with study participation. The risks of PVB are bleeding including neuraxial hematoma, infection, nerve injury, pneumothorax or pleural puncture, intravascular injection, inadvertent epidural or spinal injection, hypotension, Horner's syndrome, and failed block or inadequate analgesia. The risks of erector spinae plane blocks have not been fully described due to the infancy of the technique. Given the proximity to the paravertebral, neuraxial, and pleural spaces, the risks of erector spinae plane blocks are felt to be similar. However, due to the increased distance between the erector spinae plane and the pleura and neuraxis, these risks are thought to be decreased with an improved safety margin.

#### **15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES**

The procedural risks involved with PVB and erector spinae plane blocks will be managed according to the complication. All blocks will be performed after placement of intravenous access with adequate monitoring including continuous pulse oximetry, EKG, and noninvasive blood pressure. Resuscitation equipment will be readily available. Hypotension will be treated pharmacologically according to the degree of hypotension. Inadvertent pleural puncture will be diagnosed with chest radiography and subsequent interventions (such as tube thoracostomy) will be guided by consultation with surgery depending on the severity of the pneumothorax. Inadvertent intravascular injection will be managed according to the degree of cardiovascular compromise with intralipid readily available

during all blocks. Bleeding, neurologic, and infectious complications will be managed according to the degree of neurologic sequelae in consultation with surgery. Horner's syndrome will be managed expectantly as it recedes with the resolution of the block.

The following study procedures will be done to maintain confidentiality of this study: hard copies will be kept in a locked medical office and the patients' own medical charts. Any digitized records will be stored in encrypted files on password-protected computers.

#### **16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT**

Following study participation, all hard copies of the ICF and single-page CRF will be kept in the PI's locked office in a separate locked file cabinet. Digitized records will be de-identified using subjects' randomization numbers—only the single-page hardcopy CRF will contain identifiable personal health information as well as the randomization number. As such, subject research records will only be identified by a study number. The master list linking subject name and identifiable personal health information to subject study number will be kept in a separate locked file cabinet in the PI's locked office.

#### **17. POTENTIAL BENEFITS**

There are no known immediate medical benefits to study participation for the individual. However, future patients may benefit if we determine that one anatomic location provides greater relative benefits or fewer relative risks. In addition, current subjects may themselves benefit if they require future surgery and a postoperative analgesic.

#### **18. RISK/BENEFIT RATIO**

There are no known medical risks to subjects and the risk of confidentiality loss has been minimized. The benefits to society and future patients are potentially significant since there currently may be thousands of patients receiving less-than-optimal analgesia from providers using one of the two anatomic locations described in this protocol.

#### **19. EXPENSE TO PARTICIPANT**

None.

#### **20. COMPENSATION FOR PARTICIPATION**

None.

#### **21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES**

Principal Investigator, **Brian M. Ilfeld, MD, MS**, is a board-certified anesthesiologist with fellowship training in and 17 post-training years experience with regional anesthesia and perineural local anesthetic infusion. Dr. Ilfeld holds a license to practice medicine in California. Dr. Ilfeld has medical privileges at the UC Medical Centers. Dr. Ilfeld, or another investigator, will follow all subjects during their perineural infusion. Dr. Ilfeld will be responsible for the overall management of this study, as well as for the well-being of study subjects.

Co-investigators, **Jackie Sztain, MD, Rodney Gabriel, MD, MAS, Engy Said, MD, Bahareh Khatibi, MD, John Finneran, MD, Matthew Swisher, MD, MS, Wendy Abramson, MD, Jessica Black, MD**, are all board-eligible or board-certified anesthesiologists with fellowship training in regional anesthesia and perineural local anesthetic infusion. In addition, **Anne Wallace, MD**, is a board-certified surgeon with decades experience involving breast surgery. All hold a license to

practice medicine in California and have medical privileges at the UC Medical Centers. All will help consent subjects, perform a history and physical exam, assist in placing nerve blocks (with the exception of Dr. Wallace) and collect outcome measurements.

## **22. BIBLIOGRAPHY**

1. Naja Z, Longqvist PA. Somatic paravertebral nerve blockade. Incidence of failed block and complications. *Anaesthesia* 2001; 56: 1184-8
2. Forero M, Adhikary SD, Lopez H, Tsui C, Chin KJ. The erector spinae plane block: a novel analgesic technique in thoracic neuropathic pain. *Reg Anesth Pain Med* 2016; 14: 621-7
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4. Ilfeld BM, Madison SJ, Suresh PJ, Sandhu NS, Kormylo NJ, Malhotra N, Loland VJ, Wallace MS, Proudfoot JA, Morgan AC, Wen CH, Wallace AM. Treatment of post-mastectomy pain with ambulatory continuous paravertebral nerve blocks: A randomized, triple-masked, placebo-controlled study. *Reg Anesth Pain Med* 2014; 39: 89-96
5. Finneran JJ, Gabriel RA, Khatibi B. Erector spinae plane blocks provide analgesia for breast and axillary surgery: A series of 3 cases. *Reg Anesth Pain Med* 2018; 43: 101-2
6. Kairaluoma PM, Bachmann MS, Korpinen AK., Rosenberg PH, Pere PJ. Single-injection paravertebral block before general anesthesia enhances analgesia after breast surgery with and without associated lymph node biopsy. *Anesth Analg* 2004; 99(6): 1837-43
7. Mascha EJ, Turan A. Joint hypothesis testing and gatekeeping procedures for studies with multiple endpoints. *Anesth Analg* 2012; 114(6): 1304-17

## **23. FUNDING SUPPORT FOR THIS STUDY**

This is a PI-initiated investigation. Funding will be provided by the Department of Surgery.

## **24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT**

Not applicable.

## **25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER**

Not applicable.

## **26. IMPACT ON STAFF**

The study will not impact nursing staff as subjects will be receiving a regional analgesic in one of the two anatomic locations regardless of study participation.

## **27. CONFLICT OF INTEREST**

None.

## **28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES**

Not applicable.

## **29. OTHER APPROVALS/REGULATED MATERIALS**

None.

## **30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT**

Not applicable: surrogate consent will not be accepted.

